

Public health interventions to protect against falsified medicines: A systematic review of international, national, and local policies

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List of Abbreviations

ACT	Artemisinin Combination Therapy
ACTA	Anti-Counterfeiting Trade Agreement
AMR	Antimicrobial Resistance
API	Active Pharmaceutical Ingredient
ARD	Artemisinin derivative
CHW	Community Health Worker
CI	Confidence Interval
CODFIN	Counterfeit Drug Forensic Identification Network
DRC	Democratic Republic of the Congo
EFPIA	European Federation of Pharmaceutical Industries and Associations
EU	European Union
FDA	Food and Drug Administration
FIP	Fédération Internationale Pharmaceutique [International Pharmaceutical Federation]
FP7	European Union's Seventh Framework Programme for Research
GPHF	Global Pharma Health Fund
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
ICSR	Individual Case Safety Report
IMPACT	International Medical Products Anti-Counterfeiting Taskforce
INTERPOL	International Criminal Police Organization
IP	Intellectual Property
ISPE	International Society for Pharmaceutical Engineering
LMIC	Low and Middle Income Country
MAS	Mobile Authentication Service
MECC	Micellar Electrokinetic Capillary Chromatography
MEDQUARG	Medicine Quality Assessment Reporting Guidelines
MM	Monitoring Medicines Project
MOH	Ministry of Health
MQCL	Medicine Quality Control Laboratory
MRA	Medicines Regulatory Authority (see also NMRA). Sometimes referred to as DRA, Drug Regulatory Authority
MS	Mass Spectroscopy

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MSM	Member State Mechanism
NAFDAC	National Agency for Food and Drug Administration and Control [in Nigeria]
NGO	Non-Governmental Organisation
NMR	Nuclear Magnetic Resonance
NMRA	National Medicines Regulatory Authority (see also MRA)
PIDM	WHO Programme for International Drug Monitoring
PQM	Promoting the Quality of Medicines in developing countries
PREVENT	Preventing falsified medicines through Research, Education, Vigilance, Empowering patients and developing new Technologies (PSGH initiative)
PROTECT	Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium
PSGH	Pharmaceutical Society of Ghana
PSI	Pharmaceutical Security Institute
PSI CIS	Pharmaceutical Security Institute Counterfeit Incident System
PV	Pharmacovigilance
RFID	Radio Frequency Identification
SMS	Short Message Service [“text message”]
SP	sulfadoxine / pyrimethamine antimalarial treatment combination
SSFFC	Substandard, spurious, falsified, falsely-labelled and counterfeit medicinal products
TB	Tuberculosis
TLC	Thin Layer Chromatography
TLC-FCIS	Thin Layer Chromatography, Fast Chemical Identification System
UK	United Kingdom
UMC	Uppsala Monitoring Centre
UN	United Nations
UNODC	United Nations Office of Drugs and Crime
UNTOC	United Nations Convention against Transnational Organized Crime
USAID	United States of America Agency for International Development
WHO	World Health Organization
WWARN	World Wide Antimalarial Resistance Network

Abstract

Background

Falsified medicines are deliberately fraudulent drugs that pose a direct risk to patient health and undermine healthcare systems, causing global morbidity and mortality.

Objective

To produce an overview of anti-falsifying public health interventions deployed at international, national, and local scales in low and middle income countries (LMIC).

Data sources

We conducted a systematic search of the PubMed, Web of Science, Embase, and Cochrane Central Register of Controlled Trials databases for healthcare or pharmaceutical policies relevant to reducing the burden of falsified medicines in LMIC.

Results

Our initial search identified 660 unique studies, of which 203 met title/abstract inclusion criteria and were categorised according to their primary focus: international; national; local pharmacy; internet pharmacy; drug analysis tools. 84 were included in the qualitative synthesis, along with 108 articles and website links retrieved through secondary searches.

Discussion

On the international stage, we discuss the need for accessible pharmacovigilance (PV) global reporting systems, international leadership and funding incorporating multiple stakeholders (healthcare, pharmaceutical, law enforcement), and multilateral trade agreements that emphasise public health. On the national level, we explore the importance of establishing adequate medicine regulatory authorities and PV capacity, with drug screening along the supply chain. This requires interdepartmental coordination, drug certification, and criminal justice legislation and enforcement that recognise the severity of medicine falsification. Local healthcare professionals can receive training on medicine quality assessments, drug registration, and pharmacological testing equipment. Finally, we discuss novel technologies for drug analysis which allow rapid identification of fake medicines in low-resource settings. Innovative point-of-purchase systems like mobile phone verification allow consumers to check the authenticity of their medicines.

Conclusions

Combining anti-falsifying strategies targeting different levels of the pharmaceutical supply chain provides multiple barriers of protection from falsified medicines. This requires the political will to drive policy implementation; otherwise, people around the world remain at risk.

1. Introduction

Accurate definitions of poor quality medicines are essential. The World Health Organization (WHO) uses the umbrella term, “Substandard/ Spurious/ Falsely-labelled/ Falsified/ Counterfeit medical products” (SSFFC (World Health Organization, 2016a), sometimes shortened to SFFC), though there is no universally agreed definition for this. Previously, WHO defined “counterfeit” medicines as being, “deliberately and fraudulently mislabelled with respect to identity and/or source” (World Health Organization, 2016a). However, it has been argued that the causes and solutions of the constituent problems in the SSFFC grouping are different (Newton *et al.*, 2011a; Attaran *et al.*, 2012); in particular, “counterfeit” should not be conflated with falsified and substandard, as this may shift focus away from public health issues and more towards intellectual property (IP) concerns (Newton *et al.*, 2011a). We use the term ‘**unregistered generic**’ to refer to safe and effective medication manufactured without proper IP law authorisation. This is a legal and economic problem but does not pose a direct threat to public health, and is not a major focus in this review. In contrast, ‘**substandard**’ drugs are, “genuine medicines produced by manufacturers authorised by the National Medicines Regulatory Authority (NMRA) which do not meet quality specifications set for them by National standards” (World Health Organization, 2016a). ‘**Degraded**’ medicines were of adequate quality when they left the factory but have subsequently degraded, for example through inadequate storage or transport conditions (Newton *et al.*, 2009). We use ‘**falsified**’ to refer to medicines that have been fraudulently produced and distributed, and which do not meet the quality specifications for that drug – these are the primary focus of this review. Lastly, we use the term ‘**poor quality**’ to refer collectively to falsified, substandard, and degraded medicines, which all pose serious threats to public health.

Poor quality medicines directly harm patients by denying them access to potentially life-saving active pharmaceutical ingredients (API), or exposing them to toxins. It was recently estimated that 122,350 deaths in children under five years old in Sub-Saharan Africa were attributable to poor quality antimalarials in 2013 (Renschler *et al.*, 2015), representing 3.75% of all under-five child deaths in the region. Poor quality medicines also have pernicious consequences for communities and healthcare systems (Newton *et al.*, 2006b, 2010; Mackey and Liang, 2011; Karunamoorthi, 2014), causing lack of faith in healthcare amongst local people and providing a source of funding for organised crime networks. Of broadest consequence is the potential to promote antimicrobial resistance (AMR), now recognised as a major threat to global public health (Pisani, 2015). If poor quality medicines contain less than the intended API, pathogens can become exposed to drug concentrations in the ‘**mutation selection window**’ – high enough to exert a selection pressure but too low to kill all of the pathogens (Abdul-Aziz *et al.*, 2015). This is optimal for genetic changes that cause resistance to emerge and spread. Poor quality antimalarials are thought to be a contributing factor to the repeated evolution of antimalarial resistance in *Plasmodium falciparum* in Southeast Asia (Newton *et al.*, 2003, 2006b; Cui

et al., 2012; Bharati and Ganguly, 2013; Karunamoorthi, 2014), and to variable effective coverage of malaria case management in Africa (Galactionova *et al.*, 2015)¹. In addition, fake medicines damage the pharmaceutical industry by affecting revenue and reputation.

Although poor quality and counterfeit medicines have received increasing attention in the academic literature over the last 15 years (Fig. 1, Supplementary Methods), their prevalence is difficult to accurately determine. Poor drug quality has been reported for a wide range of anti-infectives, including antimalarials (Cockburn *et al.*, 2005; Lon *et al.*, 2006; Newton *et al.*, 2006b, 2008, 2010, 2011b; Amin and Kokwaro, 2007; Bate *et al.*, 2008; Karunamoorthi, 2014), anthelmintics (Khan *et al.*, 2010) and antibiotics (Nair *et al.*, 2011). While many studies have detected falsified drugs through pharmacological testing (World Health Organization, 2003, 2009; Dondorp *et al.*, 2004; Atemnkeng *et al.*, 2007; Sengaloundeth *et al.*, 2009; Nayyar *et al.*, 2012; Yoshida *et al.*, 2014), compilation of these data is challenging due to varying methodologies and inadequate sampling and drug analysis techniques (Taberner *et al.*, 2014). A 2013 systematic review identified 44 prevalence studies, of which 15 were defined as being methodologically high quality (Almuzaini *et al.*, 2013). The median prevalence of substandard/ counterfeit medicines was 28.5% (range 11-48%), with most studies focusing on anti-infectives in low and middle income countries (LMIC). Poor quality medicines have even been detected in the supply used by *Médecins Sans Frontières* in Kenya and in clinical trials in Tanzania and the United States of America (Cohn *et al.*, 2013; Newton *et al.*, 2015). Worldwide sales in “counterfeit and illegal medicines” have been estimated at ~US\$75 billion in 2010 (World Health Organization, 2010a). Further research is essential to better understand the scale of the problem, though it is believed to be greater in LMIC (Newton *et al.*, 2006a, 2010, 2011b) due to less stringent regulation of the pharmaceutical supply chain and marketplace. Middle income countries may be particularly vulnerable to poor quality medicines since their rising domestic production and consumption of medication runs the risk of outpacing their regulatory capacity (Mackey *et al.*, 2015c). Southeast Asia is thought to be one of the worst affected regions in the world (Newton *et al.*, 2006a, 2008).

Here, we perform a systematic review of the literature to investigate healthcare policies for tackling falsified drugs in LMIC. While poor quality medicines have been documented in high income countries (such as a major incident of falsified and counterfeit Avastin® in the United States (Cuomo and Mackey, 2014; Mackey *et al.*, 2015b)), and in treatments for non-communicable diseases (such as diabetes (Cheng, 2009)), our focus is primarily on anti-infective drug policies suitable for resource-limited settings. We describe multiple layers of intervention, targeted at the international stage, national initiatives, local pharmacies, and consumer verification at point-of-purchase. The implementation of these multi-layered efforts could reduce the global prevalence of falsified drugs and thus offer a substantial public health benefit.

2. Methods

We conducted a five-pronged approach for identifying relevant literature:

(1) A systematic search was conducted on 13/12/2015 using the criteria: (Falsified OR counterfeit OR substandard); AND (medicine OR drug); AND (policy OR policies OR intervention OR guideline OR recommendation). We searched the online databases PubMed, Web of Science, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*), with no language filters, for all studies published up to 12/12/2015. This yielded a combined total of 660 unique studies. First-round title/ abstract screening was performed independently by W.L.H. and G.L., and studies were included if they were relevant to poor quality medicines and fell into one of the following six policy themes: A: Global issues/ control efforts; B: National issues/ control efforts; C: Pharmacy-based issues/ control efforts; D: Internet pharmacy issues; E: Drug detection/ analysis techniques; F: General/ miscellaneous (but potentially relevant to anti-falsifying policies) (Table 1). Discrepancies between W.L.H. and G.L. study inclusions were resolved by group discussion. This yielded a total of 203 studies which underwent full-text analysis. We focused on papers relevant to healthcare policy, public health interventions, or pharmaceutical measures relevant to reducing the burden of falsified drugs in LMIC. Articles were excluded if they: lacked relevance to falsified medicines; did not discuss specific policies or interventions, with only a general description of poor quality and “counterfeit” medicines provided; or focused mainly or exclusively on high income countries (as defined by World Bank). 84 studies from the primary search were included in the qualitative synthesis for this review (Fig. 2, Table 1).

(2) We conducted additional searches using PubMed, Web of Science, Embase, and Google Scholar with combinations of search terms including: “falsified and counterfeit drugs”, “pharmacovigilance”, “antimalarial drug quality testing”, and “falsified drug reporting”.

(3) We checked reference lists and authors from relevant articles to identify more studies.

(4) We manually searched relevant public health or pharmaceutical online information sources, including the World Health Organization (WHO), Uppsala Monitoring Centre (UMC), Pharmaceutical Security Institute (PSI), United States Food and Drug Administration (FDA), International Society for Pharmaceutical Engineering (ISPE) Supply Chain EU Conferences, Global Pharma Health Fund (GPHF), General Pharmaceutical Council (GPhC), mPedigree/ GoldKeys, Sproxil, and PharmaSecure websites.

(5) Where necessary, study authors and organisations (Sproxil, GoldKeys) were contacted for additional information (Supplementary Methods).

In total, a further 53 journal articles, 53 website links, two books, and one correspondence with the company Sproxil were added to the 84 records retrieved from the initial systematic search for the qualitative synthesis (total: 193 citations). A quantitative meta-analysis was not performed. The systematic review flow diagram is shown in Figure 2, following PRISMA guidelines (Moher *et al.*, 2009).

3. Results

3.1. The international stage

Networks distributing falsified drugs have involved movement through multiple countries, illustrating that the problem cannot be completely addressed by working solely within any one country's borders. International collaboration allows for information sharing and warning about falsified operations (Newton *et al.*, 2008); it facilitates communication between legal departments of different countries, which is vital for successful prosecutions of larger falsified operations (Newton *et al.*, 2008); and ideally it could distribute the financial burden of tackling falsified drugs fairly between nations. Many authors (Newton *et al.*, 2002, 2006a, 2006b, 2010; Cockburn *et al.*, 2005; Attaran *et al.*, 2012) have discussed these issues; here, we highlight factors that we believe are of key importance: global reporting, leadership and international collaboration, funding, and international awareness.

3.1.1. International pharmacovigilance and global reporting

Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems (World Health Organization, 2016b). Thus, to detect falsified drugs, countries must have PV systems in place. To tackle the global problem of falsified drugs, national PV data must be fed into a global reporting system that can provide actionable intelligence to public health policy makers and legal authorities. There is currently no *mandatory* global reporting system for suspected or confirmed cases of falsified medicine (Newton *et al.*, 2014). For example, a recent major incident of falsified drugs smuggled into Angola was only publicised five months after the event on the social networking website Facebook (Newton *et al.*, 2014). Between 2002 and 2004 the WHO received no reports on falsified drugs (Newton *et al.*, 2006a).

A number of supranational organisations have emerged in an attempt to support the efforts of National Medicines Regulatory Authorities (NMRAs) in their efforts to regulate medicines in their jurisdiction, including the Pharmaceutical Security Institute Counterfeit Incident System (PSI CIS), the WHO Rapid Alert System and VigiBase, which is the database of Individual Case Safety Reports (ICSRs) from the Programme for International Drug Monitoring (PIDM) (Rägo *et al.*, 2014). The World Wide Antimalarial Resistance Network (WWARN) Antimalarial Quality (AQ) Surveyor (Tabernero *et al.*, 2014; World Wide Antimalarial Resistance Network (WWARN), 2016) provides online access to summaries of antimalarial quality reports, and is available in English and French.

WHO runs a Medical Product Alert [formerly Rapid Alert] reporting service, to which NMRAs can submit reports of poor quality medicines (World Health Organization, 2016c). Reports are published in English and French, with the intention of improving information sharing between different countries' NMRAs and alerting countries to potential problems. Only four alerts were published in 2015; as of February 2016, there have already been three published this year (falsified hepatitis C

medicines and yellow fever vaccines in Southeast Asia, and falsified phenobarbital in West Africa) (World Health Organization, 2016c). A recent analysis of PSI CIS data attempted to quantify the presence of “counterfeit drugs” in the “legitimate supply chain” (Mackey *et al.*, 2015c). However, the PSI has been criticised for keeping its industry reports on fake medicines confidential, with information inaccessible to WHO or other public health bodies, and even to other pharmaceutical companies (Cockburn *et al.*, 2005). Newton *et al.* has called for mandatory reporting on all suspected poor quality medicines to the WHO Rapid Alert System (Newton *et al.*, 2014). One strategy for achieving this is to include poor quality medicine reporting as a factor in the Access to Medicine Index, which ranks the 20 largest research-based pharmaceutical companies by their efforts to promote access to medicines in LMIC. The 2015 Access to Medicine Index Methodology stated that, “to reduce the public health dangers of suspected falsified or substandard medicines, companies should systematically report issues to national authorities and WHO Rapid Alert” (Access to Medicine Index, 2015).

In addition to active reporting services, there have been attempts to detect poor quality medicines by mining pharmacological databases, searching for ‘signatures’ of suspicious drug quality. ICSRs are packages of information relating to, “adverse events, product problems and consumer complaints,” concerning a pharmaceutical agent (US Food and Drug Administration). VigiBase is a WHO global database of compiled ICSRs (Lindquist, 2008), and receives input from the 120 member countries of the WHO PIDM. In 2012, the WHO-collaborating centre for international drug monitoring, the Uppsala Monitoring Centre (UMC), mined VigiBase data to detect signatures of poor quality medicines (Juhlin *et al.*, 2015). For example, the algorithm identified medicinal products with a higher than expected number of ICSRs. The results could then be verified by confirming with NMRAs. A similar algorithm was used by the Monitoring Medicines project (MM) (Pal *et al.*, 2015), which ran from 2009 to 2013 with the aim of improving national and international PV among its 11 member countries from across Asia, Africa and Europe. The UMC highlighted several key prerequisites for effective identification of poor quality medicines from VigiBase, including: rapid uploading of ICSRs to the VigiBase database, detailed information on the medical products for tracking distribution networks, and options for verification of suspected poor quality medicines e.g. through contacting primary reporters or accessing product samples for pharmacological analysis (Juhlin *et al.*, 2015).

National PV programmes that can feed information into multinational databases like VigiBase are still lacking in many countries worldwide. The WHO estimates that out of 46 Sub-Saharan African countries, 30% have no NMRA and a further 63% have “minimal capacities that hardly function”, leaving just 7% with “moderately developed capacity” (World Health Organization, 2015a). Similarly, an analysis of PSI CIS data between 2009 and 2011 revealed 127 of 196 (65%) countries had no legitimate supply chain CIS reports (Mackey *et al.*, 2015c). Out of 13 Arabic-speaking countries in

the Middle East region, only six (Egypt, Iraq, Jordan, Oman, Kingdom of Saudi Arabia, and the United Arab Emirates) reported having any PV programmes in place in 2013, leaving five states with no declared reporting systems and two (Lebanon and Syria) for which data were unavailable (Wilbur, 2013). The WWARN database of poor quality antimalarials did not identify antimalarial quality reports for 60.6% (63) of the 104 malaria-endemic countries investigated (Taberner *et al.*, 2014). Even for passive ICSR reporting to the WHO PIDM, of the 54 recognised sovereign states in Africa, we count 34 official members (63%) and 7 associate members in the PIDM. Thus, 20 African countries (37%) still lack official membership at time of writing, with 13 (24%) also lacking associate membership, including populous countries such as Chad, South Sudan, and Somalia (World Health Organization, 2016d). To gain PIDM membership, WHO member states must demonstrate a sufficiently functional PV programme for ICSRs to be collected and submitted (World Health Organization, 2016e). Thus, the relative underrepresentation of LMIC in PIDM membership reflects the reduced PV capacity in these countries. However, the trend for PIDM membership is encouraging: in the 11 years from 1992 to 2003, only seven African countries were official members (Ghana, Egypt, Morocco, South Africa, Tanzania, Tunisia, and Zimbabwe); in the subsequent ten years (2004-2014) a further 27 African countries became official members (World Health Organization, 2016d). The number of ICSRs reported from Africa to Vigibase grew from 2,695 in 2000 to over 25,000 in 2010 (Isah *et al.*, 2012). Nevertheless, ICSR databases will not capture all instances of drug falsification, as not all falsified drugs will lead to ICSRs even in high income countries, e.g. if treatment failures go unreported or are unattributed to medicinal quality, or if poor quality medicines are identified and seized prior to user consumption.

3.1.2. International collaboration and WHO leadership

Given the many different components of an effective anti-falsifying strategy and the need for robust promotion of reporting, a clearly identifiable and strong supranational leadership is important to coordinate different international stakeholders. The WHO would seem the natural candidate to take on a leadership role and its efforts are discussed below. However, it has been suggested that other organisations such as the UN Office of Drugs and Crime (UNODC) and the International Criminal Police Organization (INTERPOL) should also be more heavily involved in surveillance and law enforcement (Buckley and Gostin, 2013; Mackey and Liang, 2013). The UN Convention against Transnational Organized Crime (UNTOC) could also provide viable enforcement mechanisms and stakeholder engagement (Mackey and Liang, 2013).

IMPACT (International Medical Products Anti-Counterfeit Taskforce) was launched in February 2006, aiming to bring together relevant stakeholders including nation states, the pharmaceutical industry, non-governmental organisations (NGOs), and enforcement agencies such as INTERPOL to tackle “counterfeit” medicines (World Health Organization, 2016f). IMPACT focused on five policy areas: legislative and regulatory infrastructure, regulatory implementation, enforcement, technology,

and communication (World Health Organization, 2008). While conceived with good intentions, it has been argued that the emphasis was placed too heavily on IP issues rather than addressing public health concerns (Asian Community Health Action Network (ACHAN) et al., 2010). (The Council of Europe's MEDICRIME Convention has faced similar criticism (Bate and Attaran, 2010)).

The Member State Mechanism (MSM) on SSFFCs was established by WHO in the 65th World Health Assembly (WHA), aiming to: “promote, through effective collaboration among Member States and the Secretariat, the prevention and control of SSFFC medical products and associated activities” (World Health Organization, 2012). The group has met annually since 2012 (following a 2011 meeting of the ‘Working Group of Member States on SSFFC’). Specific objectives are summarised in Box 1. In the most recent meeting (November 2015), the MSM discussed the development of international information sharing resources for member states to communicate about poor quality medicines (World Health Organization, 2015b).

Box 1. Objectives of the MSM (World Health Organization, 2012)

- Identify needs and challenges
- Make policy recommendations
- Develop tools in prevention, detection, and control of “SSFFC”
- Strengthen national and regional capacities for supply chain integrity
- Facilitate consultation, cooperation, and collaboration with relevant stakeholders, including information sharing and collaboration with other WHO areas.
- Strengthen regulatory capacity and quality control laboratories at national and regional levels.

3.1.3. Funding, international attention, and global trade

Funding for anti-falsifying programmes comes from a variety of sources: home governments, multinational bodies (such as WHO), international aid (for example, Rwanda received financial support from the US government's department USAID (Nwokike and Joshi, 2009)), the pharmaceutical industry, and NGOs (Heyman and Williams, 2011). The Monitoring Medicines project was financed by the European Union's Seventh Framework Programme for Research (FP7) (Pal *et al.*, 2015) (now superseded by the EU's Horizon 2020) for €2 million. Because of the high price tag associated with these large multinational PV surveillance programmes, integrated funding between multiple sources is likely required. From 2006-2009, IMPACT was funded by WHO member states through the European Commission and the governments of Australia, Germany, Italy, and the Netherlands (total: 68%), and from WHO (28%) (World Health Organization, 2010b). Half of the €20 million PROTECT project (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium) (PROTECT) funding came from the EU, and half from participating

pharmaceutical companies in the European Federation of Pharmaceutical Industries and Associations (EFPIA). Pharmaceutical companies pay for Mobile Authentication Services (MAS) technology and labels to be appended to their products (discussed below). For example, a Nigeria-based distributor, Euromed, pays Sproxil for MAS protection of Clomid [generic name: clomifene], the most widely used ovulation induction medication in the country (Sproxil, 2016a). Sproxil has received grants from the non-profit Acumen (Sproxil, 2016a), while PharmaSecure (another MAS technology provider) has been funded by USAID and the Bill & Melinda Gates Foundation (PharmaSecure, 2015). In summary, anti-falsifying funding will likely arise from a broad mixture of sources, emphasising the need for cooperation and collaboration both between different national governments and between the private and public sectors, with a role for supranational organisational bodies such as the EU and WHO.

To secure money, time, and personnel, the issue of falsified drugs as a public health problem must be elevated in the international agenda. For example, it has been argued that recent investments in accessible medicines should be matched by drug quality assurance (Newton *et al.*, 2014). Given the relationship with international trade and law, poor quality medicines need to be ‘on the radar’ not only of public health experts, but also politicians and diplomats. An analogy can be drawn with the issue of AMR, which has made headlines internationally, and been publically highlighted by healthcare leaders such as the Chief Medical Officer of the UK, Professor Dame Sally Davis (Professor Dame Sally Davis, 2013), and the Director-General of the WHO, Dr Margaret Chan (World Health Organization, 2014), and senior political figures such as President Barack Obama (President Barack Hussein Obama, 2014). Similar international attention is needed on medicine quality and falsification.

Poor quality medicines are relevant to certain multilateral trade agreements. One example is the Anti-Counterfeiting Trade Agreement (ACTA), an international treaty that aims to enforce IP rights and combat the proliferation of counterfeit and pirated goods (Office of the United States Trade Representative, 2011). A European Commission fact sheet on ACTA stated in 2009 that, “dangerous counterfeit goods,” including pharmaceuticals, “impact on consumer protection and public health” (European Commission, 2009). As noted above, “counterfeit” unregistered generics are not inherently dangerous, provided they adhere to high safety standards; the public health threats come from falsified, substandard, and degraded [poor quality] medicines. Moreover, ACTA negotiations have largely been conducted without public access, which has attracted criticism. This makes it difficult to ascertain exactly how, if at all, ACTA will contribute to anti-falsifying public health efforts. It has also been claimed by *Médecins Sans Frontières* that ACTA will negatively affect the production and supply of safe, cheap generics (MSF Access Campaign, 2012). The European Parliament rejected ACTA in 2012 on the grounds that it was, “too vague, open to misinterpretation,” and could “jeopardise citizens’ liberties” (European Parliament, 2012). Future IP treaties should draw a clear

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distinction between unregistered generics and poor quality medicines to assist in public health efforts to safeguard medicine quality.

3.2. National initiatives: Preventing falsified drugs from entering the supply chain

The pharmaceutical supply chain encompasses everything from the factories producing a drug to the vendor selling it. The globalisation of pharmaceutical supply chains results in significant complexity, providing many entry points for falsified drugs. Even countries with tight control over medicine sales and distribution can have their efforts undermined by illegal drugs markets in neighbouring countries (Gomes *et al.*, 1998). Moreover, it has been argued that drugs manufactured for export in high-income countries – including for humanitarian work – have a lower quality control standard compared with those intended for internal use (Caudron *et al.*, 2008).

The task of regulating pharmaceutical supply chains should be undertaken by the country's NMRA. As described above, many countries lack a developed or even semi-functioning NMRA. Difficulties include budget and human resources constraints and limitations on government control and jurisdiction (Box 2). Moreover, corruption can undermine drug regulation efforts. For example, Garuba *et al.* used standardised questionnaires to assess Nigeria's pharmaceutical sector, and found it to be "vulnerable to corruption", particularly at sites of drug registration and port inspection (Garuba *et al.*, 2009). The authors called for greater action from the Nigerian government and international community to limit corruption, for example by drafting improved conflict of interest guidelines. Though Cohen *et al.* argue that direct government involvement in market authorisation, drug selection, procurement and inspection may increase opportunities for corruption (Cohen *et al.*, 2007). Thus, where initiatives to tackle falsified drugs come from central government, strong internal safeguards against corruption are required.

Box 2. Difficulties in establishing and maintaining a well-developed National Medicines Regulatory Authority

- Requirements for financing, specialist knowledge, and human resources needed to effectively monitor supply chains
- Pharmaceutical supply chains generally combine private and public ownership, making government regulation more complex
- Limitations to a country's jurisdiction; supply chains involve multiple independent international parties, making efforts to enforce legislation across the supply chain more challenging.
- Potential for corruption at multiple levels

Social and infrastructural instability, e.g. due to conflict and natural disasters, can be major impediments to successful national drug quality programmes. Severely disrupted countries, such as Afghanistan, Somalia, and the Democratic Republic of the Congo (DRC), face an especially difficult challenge in providing centralised control of drug distribution, due to weak Ministries of Health and poor donor coordination (Kohler *et al.*, 2012). A *P. falciparum* outbreak in northwestern Pakistan in 2003 was attributable to substandard sulfadoxine-pyrimethamine (SP) antimalarials (Leslie *et al.*, 2009). The outbreak occurred in a refugee camp located in the Federally Administered Tribal Areas (FATA), tribally-governed regions along the contested and porous ‘Durand Line’ dividing Pakistan and Afghanistan. The SP had been manufactured locally due to drug shortages. In another study, 32% of SP and quinine from randomly sampled public and private outlets in Afghanistan was substandard (Lalani *et al.*, 2015). Authors have highlighted a lack of pharmacist involvement in drug safety surveillance in Pakistan (Hasan and Ahmed, 2012), and chaotic supply chains lacking stable NMRA central administration in Afghanistan and Libya (Harper and Strote, 2011; Kafu, 2014). These studies demonstrate the need for greater pharmaceutical security in disrupted regions.

3.2.1. Centralising pharmaceutical control

One strategy for securing drug quality is to have tight state control over the pharmaceutical supply chain. This approach has been adopted by Rwanda, a low-income country that has had success in tackling falsified drugs, particularly anti-TB medicines (Bate *et al.*, 2012, 2013; Binagwaho *et al.*, 2013). Rwanda made several changes in the regulation of its pharmaceutical supply chain, detailed in “Guidelines for pharmacovigilance and medicine information system in Rwanda,” 2011 (Republic of Rwanda Ministry of Health, 2011). Binagwaho and colleagues describe a major focus on pharmacovigilance, with drug quality screening at importation and subsequently along the supply chain, and notification forms supplied for patients and healthcare staff to report suspicious medicines to the National Pharmacovigilance and Medicine Information Center (Binagwaho *et al.*, 2013). The Ministry of Health required manufacturers to have WHO certificates of Good Manufacturing Practices, and private pharmacies were only permitted to sell anti-TB medication provided they had been accredited as Centers for Diagnosis and Treatment of Tuberculosis. These measures are summarised in Box 3.

The Rwandan Medicines Procurement and Planning Division (MPPD) ensures that health centres throughout the country are stocked with sufficient drugs. But if this fails, individual facilities can be given permission by the Ministry of Health to procure drugs from private sources (Supply Chain Management System (SCMS), 2013). When this also fails, medicine stock-outs occur (Supply Chain Management System (SCMS), 2013; Nditunze *et al.*, 2015). The Rwandan government is aiming to address these issues as part of its, “Third Health Sector Strategic Plan” (Government of Rwanda Ministry of Health, 2012), active from 2012 – 2018. As discussed above, substandard antimalarials in Pakistan have been associated with drug shortages leading to decentralised local procurement. It

would be beneficial to investigate the relationship between poor quality medicine prevalence and drug stock-out duration and severity.

Box 3. Strategies for securing medicine quality in Rwanda

- Ministry of Health only purchased medicines produced with WHO-approved certificates of Good Manufacturing Practices.
- Pharmacovigilance sub-committees established at all health centres
- Standardised notification forms for reporting poor quality medicines available to patients and healthcare staff. The forms are reviewed by the National Pharmacovigilance and Medicine Information Center.
- Training of >2,400 health workers in guideline implementation
- Support from national and international partners
- Quality control testing on medicine imports
- Regular systematic sampling of artemisinin combination therapies (ACT) and anti-TB drugs at multiple stages along the supply chain
- Prevention of medicine degradation through climate-controlled storage and transport facilities
- Prohibition of sale of malaria monotherapies and all anti-TB medicines through private pharmacies, unless accredited as Centers for Diagnosis and Treatment of Tuberculosis by the government.
- Effective collaboration between government agencies - Bureau of Standards, Customs Services Department, and Ministry of Health for drug inspections; and if falsified drugs are found, coordination with the Rwandan police force and INTERPOL.

Adapted from (Binagwaho *et al.*, 2013).

The Rwandan model may be difficult to implement in much larger and decentralised countries such as India and DRC; Rwanda has a population of less than 12 million compared with India's 1.3 billion, and in 2014 had only 47 hospitals and 478 health centres (Republic of Rwanda, 2014). Substandard medicines have been reported in major Indian cities, which is of particular concern as many LMIC import drugs from India (Bate *et al.*, 2009b). A 2015 systematic review of poor quality medicines in India made several policy recommendations (Khan and Khar, 2015), summarised in Box 4. It is essential for countries to follow up their medicine quality improvement policies with on-going evaluation and audit, to ensure policy implementation and effectiveness.

Box 4. Recommendations for reducing the burden of poor quality medicines in India

- Harsher legal penalties against perpetrators of medicine falsifying (if the crime results in consumer death then there is a minimum ten years' imprisonment), and establishment of poor quality and counterfeit medicine specific courts
- Additional personnel to support the national medicine regulatory authority
- Central Drugs Standard Control Organization (CDSCO) publishes a list of drugs/ medical and cosmetic products deemed poor quality and/or counterfeit
- Improved central drug testing laboratories
- Inspecting drugs imported from overseas
- 'Whistle blower' scheme, in which members of the public are financially rewarded for reporting information pertaining to poor quality medicines
- Regular drug quality evaluations (e.g. in Tamil Nadu and Kerala)

Adapted from (Khan and Khar, 2015).

Successful PV requires drug testing technologies to assess chemical quality (discussed below). The pharmaceutical supply chain can also be monitored by affixing product identifiers to drug packaging that are difficult to falsify, such as 2D barcodes and Radio Frequency Identification (RFID) (Taylor, 2014). These electronically tag products so they can be traced back to a certified point of origin. While the cost of RFID tags is decreasing (down from \$0.25 per tag in 2007 to <\$0.01 in 2013), the need for adequate computing and IT software may be prohibitive in low income countries, and the technology has been slow to take off (Taylor, 2014). Inventory tracing of this kind would be especially useful for tracking imported medicines.

3.2.2. Criminal justice

There have been calls for governments to enact stronger anti-falsifying national legislation (Newton *et al.*, 2014; Attaran, 2015; Nayyar *et al.*, 2015). For example, drug falsifying is punishable by three years imprisonment and a €75,000 fine in France, four months incarceration in Norway, and six months incarceration in The Netherlands (and only after two offences) (Nayyar *et al.*, 2015). In 2004, the head of a UK counterfeit ring that produced half a million tablets per day at its peak, received five and a half years' imprisonment for copyright infringement, not for the potential threat to public health (Liang, 2006). Retributivist justice is premised on the axiom that crimes should be punished in proportion to their severity (Stanford Encyclopaedia of Philosophy). Given the potentially devastating consequences of producing and distributing falsified medicines, ranging from patient death to the public health disaster of antimicrobial resistance, there is a clear case for imposing tougher sentences

for this crime. Attaran has proposed a new *Model Law on Medicine Crime* (Attaran, 2015), which can be used as a template by individual nation states for drafting their own drug falsifying laws and punishments. China has offered financial incentives to encourage informants to come forwards, though the success of this policy has not been evaluated (Chika *et al.*, 2011). Even if these laws are introduced, governments must have the will and ability to enforce them.

3.3. Policies aimed at local pharmacy

Rwanda's strategy may not be applicable in all countries, e.g. those with large private sectors. For example, most antimalarial seeking behaviour in Kenya is private (Chuma *et al.*, 2009). This is especially important because the private sector is a key entry point for falsified and substandard medicine (Syhakhang *et al.*, 2004b; Kaur *et al.*, 2008; Onwujekwe *et al.*, 2009). Drug regulatory infringements in private drug shops (Goodman *et al.*, 2007) and pharmacies (Wijesinghe *et al.*, 2007) in LMIC are common (though these studies are small). Trials have suggested that government regulation and training programmes can improve prescribing practices in private Southeast Asian retailers (Stenson *et al.*, 2001; Chalker *et al.*, 2005). However, there are concerns that punishing all infringements could limit access to essential medicines in remote areas (Goodman *et al.*, 2007).

The International Pharmaceutical Federation (FIP) adopted official policies on combating “counterfeit medicines” in Sydney in 2003 (International Pharmaceutical Federation (FIP), 2003). A summary of pharmacy-level interventions amalgamated from FIP and other guidelines is summarised in Box 5 (Conférence Internationale des Ordres de Pharmaciens Francophones (CIOPF), 2006; Ling, 2006; Chambliss *et al.*, 2012). In addition, Chauvé argues that pharmacists directly involved in distributing falsified drugs should face disciplinary actions (Chauvé, 2008). Given that drug falsifying networks involve criminal gangs, such measures require police enforcement. In June 2007, the headquarters of the *Conseil National de l'Ordre des Pharmaciens* [National Council of the Order of Pharmacists] in Côte d'Ivoire was attacked by gunmen following attempts to limit medicine falsification (Chauvé, 2008). In December 2003, the former Director General of the National Agency for Food and Drug Administration and Control (NAFDAC) in Nigeria, Dr. Dora Akunyili, narrowly escaped an attack by gunmen in Kano (Tim Phillips, 2007)².

Box 5: Recommendations for pharmacy-level interventions

Pharmacists should:

- Purchase medications from known, reliable sources, e.g. confirm drug registration with official NMRA
- Confirm with distributors that products were purchased from reliable sources
- Examine products for suspicious appearance (e.g. using WHO Checklist)
- Monitor medicine product alerts (e.g. from WHO Medical Product Alert website)
- Report suspicious medicines to NMRA, the distributor, and the manufacturer (hopefully to ultimately be entered on global reporting systems such as WHO Medical Product Alert)
- Close gaps in pharmaceutical supply, working with NMRA, other relevant agencies and pharmaceutical industry
- Use scanning technologies for prescription and drug verification (e.g. barcodes)
- Educate themselves, co-workers, and patients on poor quality medicines (links with pharmacy training and education, and raising public awareness)
- Warn patients of risks of falsified and poor quality medicines; advise to purchase drugs from reliable sources and warn of risks in internet pharmacy
- Advise patients to report any changes in their medication efficacy or the appearance of drugs, even if they were not purchased in that pharmacy.

Adapted from (Conférence Internationale des Ordres de Pharmaciens Francophones (CIOPF), 2006; Ling, 2006; Chika *et al.*, 2011; Chambliss *et al.*, 2012)

3.3.1. Pharmacist training and support

The need for improved awareness of, and training in, pharmaceutical authenticity in private retailers was demonstrated by Khan *et al.* (Khan *et al.*, 2011a), who found that only 64.5% of drug wholesalers in Cambodia consider drug credibility and quality when accessing their products. Only 56.5% checked that the drug packaging was intact, despite this being a known source of falsified drug infiltration and proper drug packaging and storage being important for maintaining drug quality (Khan *et al.*, 2013). A recent survey of antimalarial drug quality in Cambodia – a global hub of antimalarial drug resistance (Dondorp, Arjen M, 2009; Mita *et al.*, 2009; Miotto *et al.*, 2013; Ashley *et al.*, 2014) – found that out of 291 examined artemisinin derivatives (ADs), 91 (31.3%) were outside the acceptable API concentration range ($\geq 85\%$ and $< 115\%$ of expected API) (Yeung *et al.*, 2015). Given the link between subtherapeutic drug dosing and AMR, the need for action against poor quality antimalarials in Cambodian private retail outlets is particularly pressing.

Pharmacy workers could be trained specifically on issues related to falsified drugs (knowledge of which is often poor (Syhakhang *et al.*, 2004a; Newton *et al.*, 2006a)), such as training in falsified drug identification and encouragement to purchase drugs only from government approved suppliers, e.g. those with WHO certification. The WHO Checklist (World Health Organization, 2016g) provides a standardised framework for visually assessing medicine quality which could easily be used by pharmacists and is freely available online. Checklist items include packaging characteristics such as

the container being sealed, correct manufacturer name and logo, the symbol ‘®’ following the trade name; and tablet characteristics such as uniform size, shape, coating, and markings. Improving pharmacist education and training, safety standards, and integration into the healthcare system have been highlighted as strategies to improve pharmacy practice in Yemen (Al-Worafi, 2014). In addition to pharmacists, community health workers (CHWs) could receive training on issues of drug quality and authenticity, alongside best prescribing practices; inconsistent CHW prescribing in Kenya has resulted in antimalarial under-dosing (Zurovac *et al.*, 2005). The World Health Professionals Alliance has dedicated training and campaigning resources towards falsified drugs to raise awareness of the issues for all healthcare professionals (DeCola, 2010). Pharmacists could also be trained in using low-resource drug testing equipment to screen their stock for chemical and packaging quality – these techniques are discussed below.

3.3.2. Checking drug registration

Registration to a national competent authority, such as the Department of Drugs and Food (DDF) in Cambodia, is associated with higher drug quality (Khan *et al.*, 2011b). An analysis of 1,940 essential medicines from 18 LMIC by GPHF-MinilabTM showed that medicine registration was strongly associated with drug quality: 79/1,589 (5.0%) vs 131/351 (37%) drugs failed quality testing among registered and unregistered drugs, respectively (Bate *et al.*, 2010a). Using these data, we calculate a relative risk (RR) for medicine registration of 0.13 (95% Confidence Interval, 0.10 – 0.17, $P < 10^{-70}$, χ^2 test) (Supplementary Methods). Patent Medicine Vendors (PMVs) in Nigeria use NAFDAC identification numbers to establish drug authenticity (Oladebo *et al.*, 2011). Therefore, one way of improving pharmacy-based drug quality assessment would be for governments to build their drug registration capacity, which can be limited in LMIC (Bate *et al.*, 2010b). The US Institute of Medicine has recommended such countries use the International Conference on Harmonisation Common Technical Document format for product registration (Buckley and Gostin, 2013). However, criminal drug falsifiers could attempt to forge the registration certificates.

Use of drug registration has been mixed. A 2007 joint report by the Kenyan MoH, WHO, and Health Action International-Africa found that 42% of antimalarials in Kenya were unregistered (World Health Organization, 2007). In another study in Kenya, only half of SP and amodiaquine from private pharmacists were registered with the Pharmacy and Poisons Board (PPB) (Amin and Snow, 2005) while 69.9% of a selection of anti-infectives and analgesics were registered by the Cambodian DDF (Khan *et al.*, 2011b), and just 3/21 antibiotic products used to treat Sexually Transmitted Diseases in Myanmar displayed official ‘registered’ labels (Prazuck *et al.*, 2002). In Cambodia, lack of proper registration has been associated with foreign-manufactured products, suggesting that stronger regulations on drug importation and/or port inspection and quality testing could be important (Yoshida *et al.*, 2014).

3.3.3. Internet pharmacy

Internet pharmacy is becoming increasingly prevalent. Drugs recalled or restricted from the open market are available for purchase online, and may be poor quality (Tawab *et al.*, 2007; Veronin and Nguyen, 2008; Veronin, 2011; Veronin *et al.*, 2014; Mackey *et al.*, 2015a). Most of the literature on this topic identified through our search concerned online sales in high income countries such as Japan (Khan *et al.*, 2012; Takahashi *et al.*, 2013), North America (Veronin *et al.*, 2007; Bate and Hess, 2010; Mackey and Liang, 2012), and Europe (European Commission, 2006; Tawab *et al.*, 2007). Antiretrovirals and medications for opportunistic infections can be purchased online (Wang *et al.*, 2015), and internet pharmacy seems likely to become increasingly common in LMIC. In the UK, all pharmacies, including online sales, must be registered with the General Pharmaceutical Council, the Medicines and Healthcare Products Regulatory Agency (MHRA), and must display an EU Common Logo on every page of their website (General Pharmaceutical Council, 2016). Registration (e.g. with the NMRA), monitoring and shutting down fraudulent websites, and increasing public awareness will be important in protecting people from poor quality online pharmacy.

3.3.4. Raising public awareness

In Nigeria, public awareness of fake medicines was raised through meetings of village leaders, posters and leaflets, billboards, and even prize-giving ceremonies in schools for students who learn how to identify fakes (Tim Phillips, 2007). Survey data from Cotonou, Benin, suggests that TV and radio campaigns can be effective at increasing awareness (Abdoulaye *et al.*, 2006). Online resources and social media can also be used, for example *Fight The Fakes* and SafeMedicines.org (created by the Partnership for Safe Medicines) (Fight The Fakes, 2016; SafeMedicines.org, 2016). These efforts can augment other anti-falsifying strategies, particularly the consumer authentication methods described below, which require consumer actions at point-of-purchase. Any public health messaging must be done in a way that is mindful of the local socio-political and cultural context to ensure maximum impact.

3.4. Drug analysis and point-of-purchase verification technologies

An essential component of any anti-falsifying strategy is the ability to detect falsified drugs, by chemical or other means. Sophisticated forensic analysis of drug samples and packaging has led to the interruption of trade in falsified medicines entering Southeast Asia (Newton *et al.*, 2008). However, to tackle the problem on a larger scale, solutions have to be developed that meet the requirements of resource-limited settings in LMIC. The Promoting Quality Medicines in Developing Countries (PQM) program aims to increase the use of such novel technologies in LMIC for detecting falsified and substandard drugs (U.S. Pharmacopeial Convention). After being established in 2009, the budget more than tripled in 2013, from \$35 million to \$110 million.

Here, we define two broad concepts of drug testing in LMIC: low-resource drug testing and consumer authentication methods (Table 2). Low-resource drug testing systems are targeted at local pharmacists or trained inspectors such as police and customs officers, who can screen products arriving at ports (where falsified drugs have been detected (Nair *et al.*, 2011)), or other drug storage and transportation hubs. This equipment can either be used to test suspicious drugs or as part of stock sampling and market surveillance, and may form part of national anti-falsifying and PV programmes (requiring an efficient system for passing information up to NMRAs). The utility of this approach was recently demonstrated when GPHF-MinilabTM testing raised suspicion over the authenticity of a large batch of anti-infective medicines arriving from China to Luanda in Angola (Newton *et al.*, 2014). 1.4 million medication packets were seized, including packaging claiming to contain artemether-lumefantrine (an artemisinin-combination therapy (ACT) and front-line antimalarial) and mebendazole, an anthelmintic. No API was detectable in either case, and the characteristic yellow colouration of artemether-lumefantrine was imitated using yellow pigments. Newton and colleagues have proposed a checklist of Medicine Quality Assessment Reporting Guidelines (MEDQUARG) that can be followed when reporting drug quality surveys (Newton *et al.*, 2009). Items include survey details, sampling design, outlets sampled, who conducted the sampling (did they know the sellers?), methods of drug chemical and packaging analysis, and blinding.

A consumer authentication tool is a system designed to allow every consumer to easily and quickly test the drugs that they are about to buy to verify their authenticity, preferably at point of sale. This is particularly applicable to the market-stall pharmacist setting, and represents the ‘final barrier’ protecting people against poor quality medicines if all other measures have failed.

3.4.1. Low resource drug-testing

A number of simple API tests have been developed in recent years, particularly for analysing antimalarial drug authenticity (Ioset and Kaur, 2009; Koesdjojo *et al.*, 2014; Green *et al.*, 2015; Ho *et al.*, 2015). Kovacs *et al.* conducted a systematic review of technologies for drug testing applicable in LMIC (Kovacs *et al.*, 2014). The authors identified 42 technologies, and followed the Counterfeit

Drug Forensic Identification Network (CODFIN) workflow as a template for categorisation. They assessed suitability for LMIC based on a scoring system from 0-8, with considerations such as low cost, minimal sample preparation, consumption of laboratory supplies, speed and ease of use, limited training requirements, and portability. Techniques identified as ‘highly applicable’ to LMIC (with scores out of eight) were: Counterfeit Device #3, CD-3 (8), Fourier Transform Infrared spectroscopy, FTIR (8), Raman Spectrometry (7), Near Infrared Spectroscopy, NIR (7), Paper chromatography cards (6), WHO Checklist (6), and PharmaCheck (6). The WHO Checklist is described above (World Health Organization, 2016g). PharmaCheck is a new technique being developed at the University of Boston; it has not yet been published and made available so details are currently limited. The remaining technologies are described below, along with the GPHF-MiniLabTM given its widespread use. Other reviews provide more technical details (Kaur *et al.*, 2010; Kovacs *et al.*, 2014); here, we give a brief description of the types of equipment currently available.

The FDA CD-3 Scanner is a handheld drug scanner that visually inspects sample drugs and their packaging, and compares them against genuine references using a range of light wavelengths. Falsified packaging or tablets should differ from the real products under at least one of the wavelengths tested, even if they appear indistinguishable with the naked eye (United States Food and Drug Administration, 2013). The scanner requires only basic training and no specialist skills. There is no need for chemical reagents; the only requirements are genuine drug products for comparison and a power supply for battery recharge. This makes it faster and more convenient than chemical tests; though one disadvantage is that there is no direct testing of API. Combined with its small size, the scanner is well suited for low-level screening for law enforcement officers or local pharmacists. In one performance test, a pharmacist and two drug inspectors received 1.5 days of training and blindly analysed 203 real and falsified antimalarial tablets, obtaining detection sensitivity and specificity of 98.4% and 100% respectively and inter-operator agreement of 100% (Ranieri *et al.*, 2014). While these results are promising, it is important to investigate a greater range of drug products under field conditions.

NIR, Raman, and FTIR are spectroscopic methods that compare electromagnetic properties of test drugs against a reference. FTIR and NIR analyse the patterns of infrared light absorption and emission from test drugs, while Raman uses the Raman scattering properties of molecules when illuminated by a laser. The techniques require little or no sample preparation, no laboratory reagents, only basic laboratory technician skills, and are fast. However, the kits are expensive (~\$50,000 (Bate *et al.*, 2009a)), with NIR having the best test performance followed by Raman (Kovacs *et al.*, 2014).

Paper chromatography cards are pre-printed cards that perform multiple lanes of chemical paper chromatography to test for the presence of chemical groups found in specific drugs, and for known substitute pharmaceuticals found in falsified drugs (e.g. aspirin in ‘antimalarials’) (Weaver *et al.*,

2013; Weaver and Lieberman, 2015). The cards have been used to identify falsified β -lactam antibiotics (Weaver *et al.*, 2013), anti-TB drugs (Weaver *et al.*, 2013), and a range of antimalarials (Weaver and Lieberman, 2015) in the field. The test only requires the sample to be dissolved in water, so there are no expensive or dangerous reagents to store and training is relatively straightforward. Compiling the multiple chemical lanes used for each sample produces a unique 'colour bar code' which can be compared against reference libraries of known pharmaceuticals.

The GPHF-MinilabTM is a mobile laboratory entirely contained in two protective suitcases (Global Pharma Health Fund, 2016), which claims to be able to test 80 compounds including drugs for priority diseases. It can facilitate disintegration tests and thin layer chromatography, and includes guides to visual inspection (Global Pharma Health Fund, 2016). It does need basic analytical chemistry skills or some specific training to operate, and each kit costs €3,109 plus reference standards and an estimated €700-900 for shipping – comparatively cheap given the kit's functionality. It has been a useful tool for government agencies as part of national anti-falsifying PV programmes (e.g. for drug screening from sampled pharmacies (Visser *et al.*, 2015), and/or screening imports at entry ports (Risha *et al.*, 2008)), and could be used by trained, large distributive pharmacists. Although less expensive than competitor testing options such as Raman and NIR, sensitivity and specificity is reportedly lower (Kovacs *et al.*, 2014). In one study, the GPHF-MinilabTM protocol awarded a 'pass' if >80% expected API was present, compared with >95% for NIR and Raman (Bate *et al.*, 2009a). Other API testing techniques highlighted as feasible for LMIC by Kovacs *et al.* (i.e. LMIC suitability score ≥ 5) were Planar Thin Layer Chromatography (TLC) Speedy Apparatus, TLC-Fast Chemical Identification System (FCIS), and refractometers (Kovacs *et al.*, 2014).

In addition to local chemical analysis in LMIC, drug samples could also be sent to national or international laboratories for confirmatory testing and forensic investigation. The WHO maintains a list of Prequalified Medicine Quality Control Laboratories (MQCL) that meet standards required for accurate analysis (World Health Organization, 2015c). As of 19th November 2015, this includes laboratories in six African countries: South Africa, Algeria, Kenya, Zimbabwe, and Uganda (World Health Organization, 2015c). As centralised hubs, MQCL can contain more expensive, resource-heavy, and labour-demanding equipment than local, portable kits like GPHF-MinilabTM; examples include packaging analysis with atomic force microscopy, and chemical analysis with Gas Chromatography Mass Spectroscopy (GC-MS) and High Performance Liquid Chromatography Mass Spectroscopy (HPLC-MS). At a typical unit cost of \$350,000-\$375,000, with substantial expertise and maintenance requirements, these technologies may be out of reach for many LMIC, but could be used in reference laboratories covering multiple states. For example, in the Lalani *et al.* study of antimalarial quality in Afghanistan, drugs were initially screened by GPHF-MinilabTM disintegration tests in Kabul, with a subset undergoing dissolution testing at a bioanalytical laboratory in London, UK (Lalani *et al.*, 2015). MQCL can perform tests specifically designed for important or commonly

encountered drugs, such as reversed-phase-HPLC to analyse fixed-dose combination artesunate–amodiaquine (a commonly used ACT), in South Africa (Le Vaillant *et al.*, 2012).

In summary, a range of affordable and scalable products using innovative new technologies are becoming available to identify falsified and substandard drugs in LMIC. A crucial step is to conduct methodologically rigorous trials comparing these different technologies, collecting data on their sensitivities and specificities for detecting different types of poor quality in different drugs, their operational strengths and weaknesses in the field, and cost effectiveness. New technologies must be continuously evaluated as they enter the market.

3.4.2. Consumer authentication

How can individual consumers distinguish between genuine and falsified medical products? Consumers may use a variety of clues, including pharmacy characteristics, drug packaging, the appearance of the tablets themselves, and drug costs; indeed, the WHO Checklist could be used by consumers as well as pharmacists. Studies using “covert shoppers” in LMIC have found that substandard medicines were 10-18% cheaper than non-failing medicines (Bate *et al.*, 2011, 2015), though there was no significant price difference between falsified and non-failing medicines (Bate *et al.*, 2015). This may be because falsifiers are deliberately trying to deceive purchasers by mimicking genuine drugs, and therefore try to price them similarly. Likewise, falsified drugs were more likely to appear locally registered than were substandards. Subjective shopper impression of whether pharmacies looked “good” or “poor” also correlated weakly with medicine quality, though the discrimination lacked sensitivity and specificity. People should not be discouraged from purchasing cheaper medicines under the belief they are poorer quality; to the contrary, the supply of cheap generics in LMIC should be increased to promote treatment coverage. Instead, more reliable signifiers of drug quality are needed for people to accurately identify genuine products, including cheap generics, and distinguish them from poor quality fakes. Some potential examples are discussed below.

3.4.2.1. Holograms

Holograms on packaging are a common strategy currently in widespread use that allow consumers and local medicine distributors to test drug authenticity. Much like banknotes, the hologram contains unique detail that is difficult to fake at high resolution. However, counterfeiters have produced sophisticated hologram imitations that can easily fool the untrained naked eye (Newton *et al.*, 2003, 2008). If fakes are only identifiable by experts equipped with a microscope then it defeats the purpose of the hologram and other technologies should be evaluated (Newton *et al.*, 2008).

3.4.2.2. Mobile Authentication Services (MAS)

An innovative solution to falsified drugs is for consumers to verify drug authenticity at point-of-purchase using mobile authentication services (MAS), for example with mPedigree GoldKeys (mPedigree GoldKeys, 2016; mPedigree Network, 2016), Sproxil (Sproxil, 2016b), and

PharmaSecure. Pharmaceutical manufacturers place a hidden code on drug packaging, which can only be revealed by scratching at purchase. This ensures that any tampering with the code can be easily detected by eye due to the damaged scratch-code. When a consumer buys the drugs, they can send this code by text message (SMS) to a secure hotline and receive SMS confirmation of product verification (Fig. 3). Sproxil's website reports that >20 million verifications have been processed to date (Sproxil, 2016b), with the number of verifications per year increasing³. The Nigerian NAFDAC is aiming for all antimalarials and antibiotics in the country to use approved MAS (National Agency for Food and Drug Administration and Control, 2014).

One advantage of this technology is its accessibility, because no specialist equipment is required and there is no need for a separate distribution network. Mobile phone use is surging in Southeast Asia (ROA Holdings, 2015) and Africa (Pew Research Center, 2015); mobile phones are now as common in South Africa and Nigeria as they are in the United States (Pew Research Center, 2015). There is minimal requirement for training, and MAS results are available immediately so authentication can be performed at the pharmacy. In addition, data collected from this system could be fed into reporting and surveillance networks, and so help target falsifying hotspots or provide baseline data for public health projects.

GoldKeys and Sproxil have both expanded into other LMIC across multiple continents, including Nigeria, Kenya, India, and Pakistan. Both companies work in partnership with pharmaceutical and telecommunication companies to provide the packaging scratch-codes and messaging services respectively. GlaxoSmithKline uses Sproxil's MAS for Ampiclox® (ampicillin plus cloxacillin) in Nigeria (Pesic, 2011). In 2014, the Pharmaceutical Society of Ghana (PSGH) launched the PREVENT initiative, which aims to Prevent falsified medicines by increasing Research, Education, Vigilance, Empowering patients and developing new Technologies (PREVENT, 2016). PREVENT aims to work with mPedigree to promote the GoldKeys platform for consumer medicine authentication in Ghana and increase MAS coverage (PREVENT, 2016).

In principle, MAS could be a significant contribution to the anti-falsifying armamentarium and link with other "mHealth" initiatives. For example, text messaging can improve patient adherence to poly-antimicrobial therapies, as used in HIV and TB treatment, with tailored incentives and reminders (Free *et al.*, 2013; Finitis *et al.*, 2014; Liu *et al.*, 2015; PharmaSecure, 2015). Mobile phone applications are addressing a wide range of non-pharmaceutical problems, with great potential for further innovation; for example, Sproxil verification of agri-business product authenticity (Sproxil, 2016c), and the provision of up-to-date information on agricultural market prices using mFarm (mFarm, 2016), have both been used in rural Kenya. Encouraging the spread of this technology in LMIC (and subsidising the infrastructure) could therefore prove extremely valuable for both public health and socioeconomic development initiatives. However, PubMed searches for 'mPedigree [All

Fields]', 'GoldKeys AND (counterfeit OR falsified) [All fields]', and 'Sproxil' [All fields], currently yield no results. Further research is needed to evaluate how often the verification codes are used for different medicines, the proportion of the population that are aware of their existence, any vulnerabilities to 'hacking' or corruption, and what actions consumers take when codes are returned as invalid.

4. Summary and Discussion

4.1. Summary

Healthcare policies can protect vulnerable patients from falsified medicines by acting at multiple levels: the international stage, national initiatives, local pharmacy, and consumer verification at point-of-purchase. The major policy points of this review are summarised in Figure 4.

4.2. Discussion

Poor medicine quality directly harms patients and has a broader negative impact on healthcare systems. In this article, we have tried to reflect the complexity of the falsified drugs problem in the multiple levels at which interventions can be targeted. Our focus has been on public health strategies that can prevent or limit falsified medicines from harming patients and the community. This reflects concerns that some efforts have emphasised IP law aspects of drug counterfeiting at the expense of reducing harm caused by poor quality medicines. These are multifaceted problems that require a multidisciplinary approach aimed at tackling both public health concerns and the legal consequences of IP law violation. Effective collaboration between different stakeholders, including law enforcement agencies, public health bodies, and the pharmaceutical industry, is therefore essential.

A recent systematic review on the prevention of “drug counterfeiting” found that the overall quality of evidence for any of the interventions assessed was low, highlighting the need for more research into this area to allow policy decision-making to be evidence-based (El-Jardali *et al.*, 2015). Low-quality evidence suggested that effective strategies include medicine registration and WHO-prequalification of drugs, while licensing of drug outlets appeared less effective. Research should evaluate policy implementation and adherence to guidelines (e.g. through audit), and the success of medicine quality interventions, e.g. by measuring changes in poor quality medicine prevalence through random sampling or the number of incidents reported to WHO. Direct comparisons of drug testing equipment should also guide policy makers on equipment selection.

Given the nature of the problem, it seems likely *a priori* that successful anti-falsifying measures will operate at multiple levels, encompassing centralisation of an international drug falsifying reporting network, government policies to strengthen national medicine screening and PV programmes, pharmacy retailer training and awareness, and retailer- and/or user- product authentication systems (Wertheimer *et al.*; Shrivastava *et al.*, 2014) (Fig. 4). Such a multi-layered approach reduces the likelihood of a ‘Swiss Cheese’ event, in which holes in different safety barriers align independently to cause a safety breach (Reason, 2000). For example, if falsified medicines were not identified at entry ports by national PV programmes (e.g. using GPHF-MinilabTM screening), then they could be stopped by trained pharmacists who recognised fraudulent or non-WHO-certified products (e.g. using the WHO Checklist), or by the consumer through MAS technologies at point-of-purchase. Each barrier

provides another layer of protection, shielding vulnerable patients from the potentially life-threatening consequences of falsified drugs. Indeed, El-Jardali *et al.* reported that such “multifaceted interventions” are effective, though the quality of available evidence was low.

The implementation of robust medicine quality control measures is an essential component of global public health. In *P. falciparum* malaria parasites, mutations in the gene *kelch13* associated with artemisinin resistance have been detected at low frequency in Africa, despite the high efficacy of ACT in that region currently (MalariaGEN Plasmodium falciparum Community Project, 2016). This suggests that artemisinin resistance could emerge rapidly in Africa if resistance is sufficiently advantageous for the parasites there. Safeguarding high antimalarial quality, and promoting optimal prescribing practices and patient adherence, may therefore contribute to preventing mutations that confer artemisinin resistance from “taking off” in African parasites. The loss of artemisinin-based therapies in Africa would be a public health disaster.

There are several limitations to this review. We did not consider poor quality medicines in high income countries such as the USA and EU member states. In an increasingly interconnected world, in which the socioeconomic divide between “Western” countries and other nations is reducing, this is somewhat artificial. We focused primarily on falsified drugs rather than other aspects of the WHO “SSFFC” umbrella. In particular, substandard and degraded medicines pose a direct threat to patient safety, possibly even greater than that of falsified drugs in LMIC, and should be addressed in public health programmes (Caudron *et al.*, 2008; Tremblay, 2013). We did not discuss non-tablet healthcare products that can also be falsified or substandard, such as inhalers (The Pharmaceutical Journal News Team, 2011), or poor quality recreational drugs (e.g. tobacco cigarettes (Stephens *et al.*, 2005)). The literature on poor quality medicines in LMIC is biased towards anti-infectives, particularly antimalarials, and this is reflected in our review. As middle-income countries such as Ghana undergo sociodemographic changes, they can face a ‘double burden’ of both infectious diseases (malaria, HIV, TB, *etc*) and chronic illnesses (cancer, cardiovascular disease, diabetes, *etc*) (Agyei-Mensah and de-Graft Aikins, 2010). Safeguarding the quality of commonly used medicines for non-communicable chronic illnesses such as statins, antidiabetics, and antihypertensives will be of increasing relevance to these countries.

This review has highlighted the complexity of international and national arrangements in place to counteract falsified drugs. A clear commitment and comprehensive plan to tackle the public health impact of poor quality medicines is called for, particularly from WHO. Governments, supranational organisations, the pharmaceutical industry (including generic manufacturers), NGOs, and healthcare professionals must unite to create a streamlined pharmacovigilance network and referral pathway involving an international system such as WHO Medical Product Alert for poor quality medicine reporting. Enforcement agencies such as INTERPOL can work with the support of judiciaries around

the world to track and bring to justice those who create and distribute falsified drugs, with national legislation enabling legal institutions to impose appropriate punitive sentences. Clear guidance and support to ensure safe supply chains through drug quality testing and the maintenance of robust pharmacovigilance is essential. Lastly, our review highlights the increasing role for local pharmacists and the consumer to maintain medicine quality at point-of-purchase through innovative technologies and authentication methods, capitalising on the rise of mobile phone usage in many LMIC. These combined efforts would tackle the global public health threat posed by falsified medicines.

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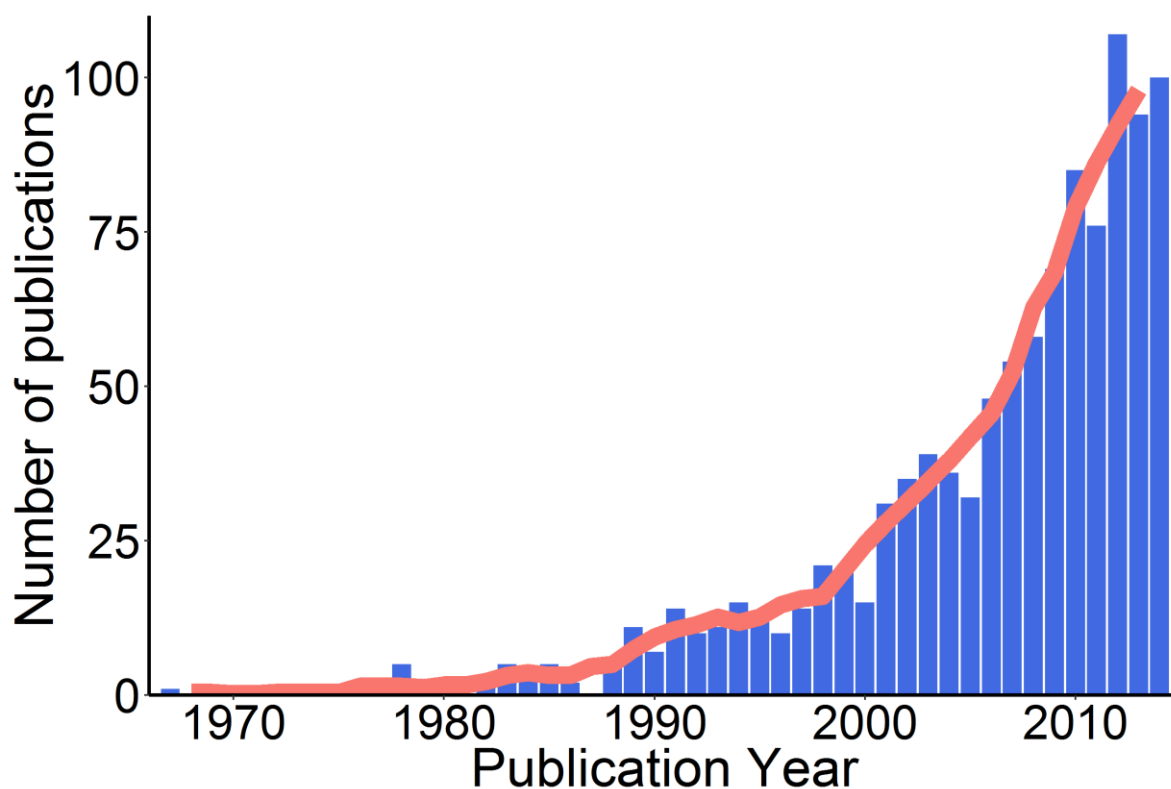
Figures

Figure 1. Poor quality medicines in 50 years of academic literature. The PubMed online database was searched for articles on falsified, counterfeit, and substandard drugs or medicines from the last 50 years (detailed search criteria in Supplementary Methods). This yielded 1,172 studies, plotted here by year (bars) with 5-year rolling average (line). The search terms are almost completely absent from the literature until 1990. 804/1,172 (69%) of the last half-century worth of publications retrieved from this search were published within the last ten years.

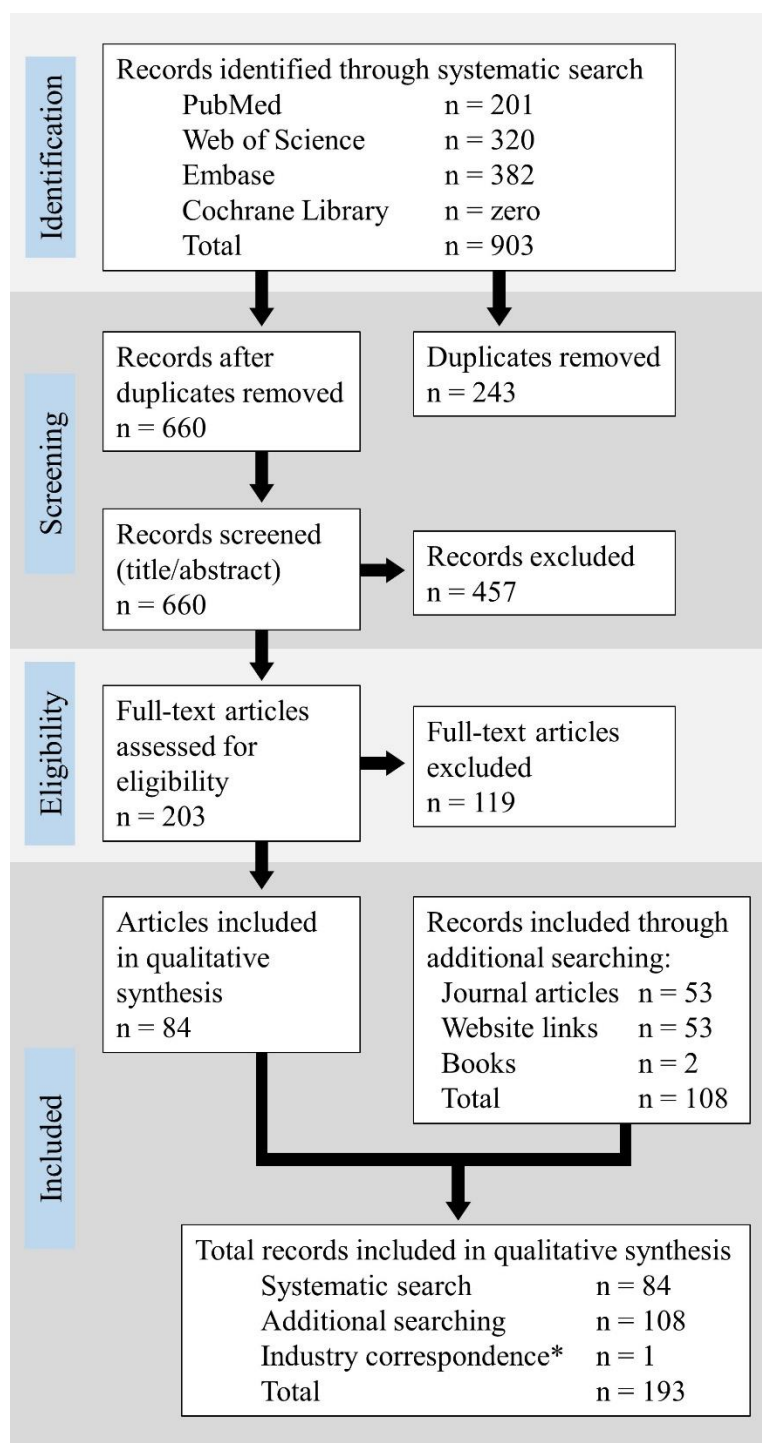


Figure 2. Systematic review flow diagram, based on PRISMA guidelines. * One reference to industry correspondence refers to communication with the company Sproxil (details in Supplementary Methods).

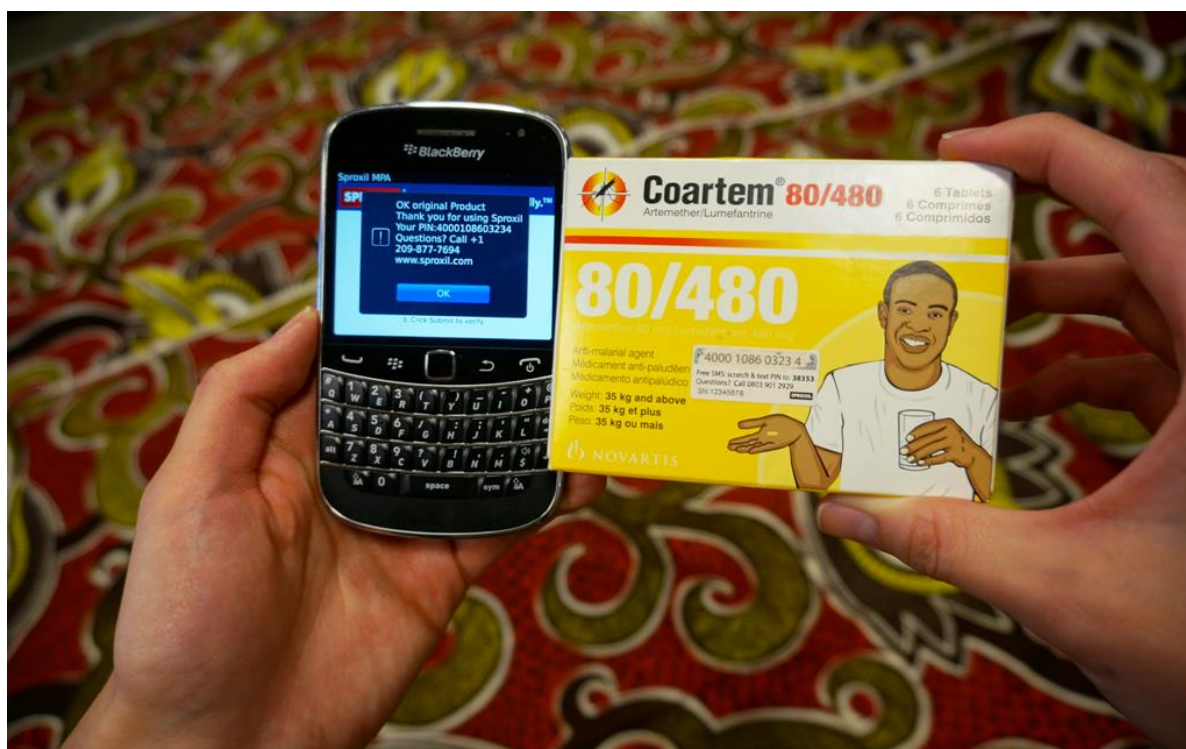


Figure 3. Sproxil Mobile Authentication Service (MAS). Photograph showing the scratch-off verification code on a Coartem® package (a front-line artemisinin combination therapy), and the verification text message sent from Sproxil. Image courtesy of Sproxil.

Public health interventions to protect against falsified medicines

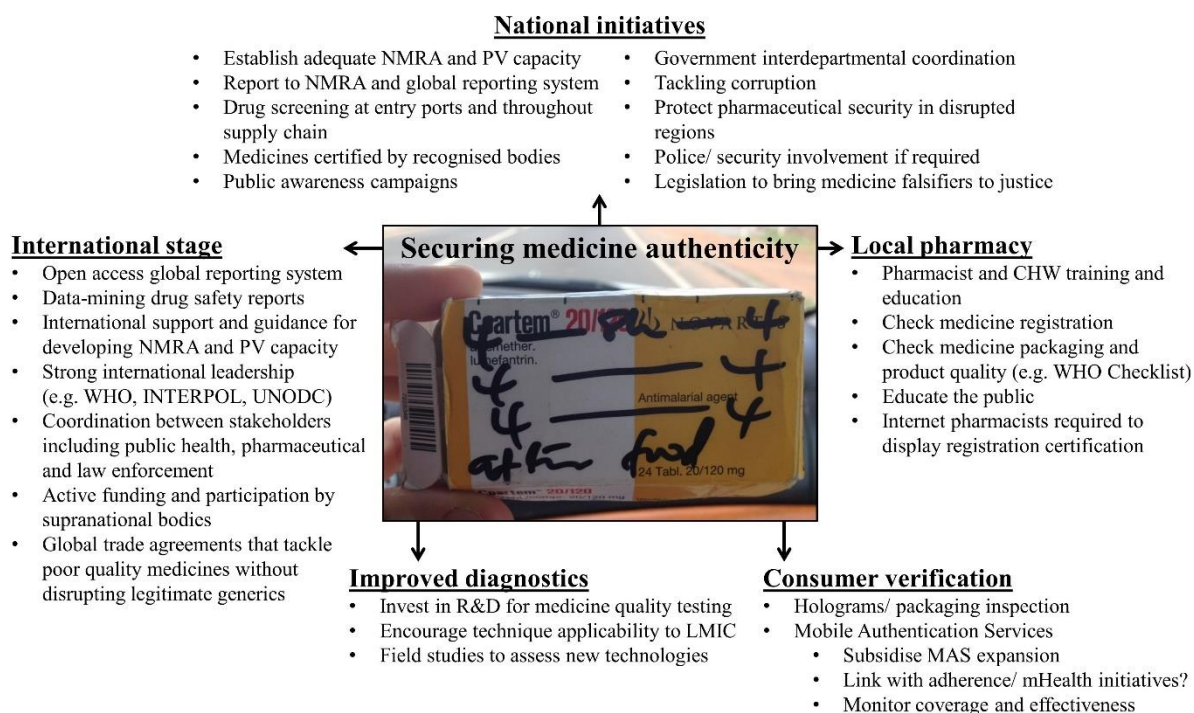


Figure 4. Summary of ant-falsifying strategies. Healthcare policies can protect vulnerable patients from falsified drugs by acting at multiple levels: the international stage, national initiatives, local pharmacy, and consumer verification at point-of-purchase. Improved drug quality testing equipment, applicable to LMIC settings, are vital at multiple stages along this supply chain. Any safety barrier may not be 100% effective, but having multiple layers of defence will make it less likely that a patient will consume poor quality medicines and hence suffer negative health consequences. NMRA: National Medicines Regulatory Authority; PV: Pharmacovigilance; CHW: Community Health Worker; WHO: World Health Organization; MAS: Mobile Authentication Services; R&D: Research and Development; LMIC: Low and Middle Income Country; INTERPOL: International Criminal Police Organization; UNODC: United Nations Office of Drugs and Crime. Photograph shows a packet of the antimalarial Coartem® from Accra, Ghana, with dosage instructions written by the physician. Image credit: William L. Hamilton.

Tables

	Theme name	Theme description	Studies included	
			First-round	Cited
A	Global	Multi-national or supranational issues, control efforts, and agencies e.g. the World Health Organization, United Nations, European Union, Africa- and Asia- wide issues, <i>etc.</i>	38	18
B	National	Issues or control efforts focused on specific nation states or sub-regions within one nation state, including state government control programmes.	51	26
C	Pharmacy	Issues or control efforts focused on pharmacists and the pharmacy retailer.	12	6
D	Internet security	Studies concerning pharmaceutical products purchased online via internet suppliers.	19	9
E	Drug analysis and verification techniques	Studies related to techniques for analysing pharmaceutical products or packaging, e.g. chemical analyses of active pharmacological ingredients, packaging inspection methods, <i>etc.</i>	32	11
F	General or miscellaneous	Studies relevant to poor quality medicines but without clear classification to the above groupings, e.g. overviews of fake drugs.	51	14
TOTAL			203	84

Table 1. Citation themes for classifying retrieved literature. Search strategy is defined in the main text (Methods), and yielded 660 unique studies of which 203 met inclusion criteria on title/abstract screening: relevance to poor quality medicines and falling within one of six policy themes A-F (defined in table, study breakdown in ‘First-Round’ column). Studies relevant to multiple themes were assigned a ‘primary’ theme and counted as such. Full-text analysis of the first-round retrieved literature yielded the final selection of 84 papers included in the qualitative synthesis and cited in this review (study breakdown in ‘Cited’ column).

Requirements:	Low-resource	medicine	Consumer authentication
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Public health interventions to protect against falsified medicines

	testing	
Potential users:	Responsible officials e.g. import inspectors, local police officers, pharmacists, <i>etc.</i>	All customers at risk
Time:	Should gain results within a reasonable timeframe (minutes-hours)	Fast enough to test at point of purchase (seconds-minutes)
Equipment required:	Equipment should be appropriate for low-resource settings.	Very minimal or widely available (e.g. mobile phone)
Replenishment or resupply:	Ideally easy to procure items in a low-resource setting	Included with packaging and disposable
Training required:	Low training requirements that do not impact primary role	None as it should reach all consumers
Sensitivity:	System should be accurate enough to warrant further action and be useful for surveillance	System is intended to be a screening tool for the consumer

Table 2. Low resource medicine testing and consumer authentication methods

Footnotes

¹ Poor quality antimalarials may result in people being inappropriately switched to second-line drugs due to treatment failure, on the assumption that the first regimen was ineffective. This is sub-optimal for patients and is not best prescribing practice for preventing antimicrobial resistance.

² Dr. Dora Akunyili is attributed as saying that, “malaria can be prevented, HIV/AIDS can be avoided and armed robbery may kill a few at a time, but fake drugs kill *en masse*” (Karunamoorthi, 2014).

³ Sproxil verification figures up to the dates shown:

- Jan 25, 2012 - 1 million verifications
- July 24, 2012 - 2 million verifications
- August 13, 2013 - 5 million verifications
- July 1, 2014 - 10 million verifications
- October 20, 2015 - 20 million verifications

Source: personal correspondence with Sproxil. The majority of these verifications are for pharmaceutical products, though Sproxil also operate in other markets such as agri-business, clothing, oil and gas, *etc.*